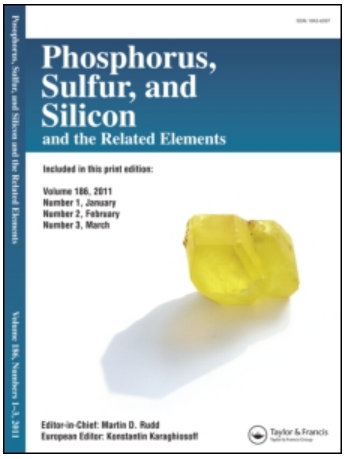

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Avijit Banerji[a]; Pizush Kanti Biswas[a]; Debasish Bandyopadhyay[a]; Maya Gupta[a]; Thierry Prangé[b]; Alain Neuman[b]

[a] Centre of Advanced Studies on Natural Products Including Organic Synthesis, Department of Chemistry, Calcutta University, Kolkata, India [b] Centre Universitaire, Orsay Cedex, France

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Synthetic Studies on 2*H*-Thiopyran Compounds: A Reinvestigation of the Reaction Between Benzaldehydes and Sodium Sulfide

Avijit Banerji,[1] Pizush Kanti Biswas,[1] Debasish Bandyopadhyay,[1] Maya Gupta,[1] Thierry Prangé,[2] and Alain Neuman[2]

[1]Centre of Advanced Studies on Natural Products Including Organic Synthesis, Department of Chemistry, Calcutta University, Kolkata, India

[2]Centre Universitaire, Paris-sud, Batiment 209D-BP34, Orsay Cedex, France

An investigation regarding the synthesis of 2H-*thiopyran compounds from substituted benzaldehydes with sodium sulfide ($Na_2S{\cdot}10H_2O$) in aqueous ethanol was carried out. The structural elucidation of the products was performed by spectroscopic methods and in one example as X-ray crystallographic analysis. A plausible mechanistic pathway is also proposed that is entirely different from an earlier report.*

Keywords Benzaldehyde; microwave irradiation; NMR; sodium sulfide; 2*H*-thiopyran; X-ray crystallography

INTRODUCTION

Sulfur chemistry constitutes a major branch of organic chemistry, among which thiopyran compounds in particular possess enormous medicinal, as well as biological and industrial, importance. Thiopyran compounds have a wide range of applications such as sensitizers,[1] key intermediates for pharmaceuticals,[2] insecticides,[3] herbicides,[4] polymer

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The present affiliation for P.K.B. is BCSIR Laboratory, Dhanmondi, Dhaka, Bangladesh.

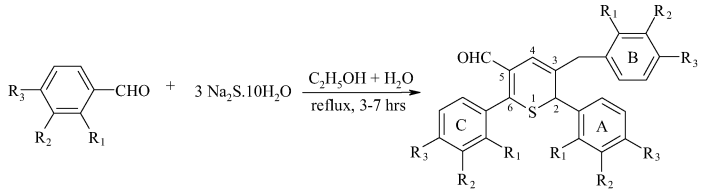
The present affiliation for D.B. is Department of Chemistry, The University of Texas–Pan American, Edinburg, Texas, USA.

Address correspondence to Avijit Banerji, Centre of Advanced Studies on Natural Products Including Organic Synthesis, Department of Chemistry, Calcutta University, 92 Acharya Prafulla Chandra Road, Kolkata 700009, India. E-mail: ablabcu@yahoo.co.uk

initiator,[5] plant protective agents,[2] and juvenile hormones.[6] Different types of thiopyran compounds have been synthesized in the recent past.[7–10] However, except for a few cases,[11–13] 2*H*-thiopyran compounds have not yet been thoroughly investigated. Latif et al.[14] reported that when benzaldehyde reacted with sodium sulfide in aqueous ethanol, it gave 3-benzyl-2,6-diphenyl-2*H*-thiopyran-5-carboxaldehyde in good yield. Cremer and Subbaratnam[15] proposed a probable mechanism where cinnamaldehyde was postulated as an intermediate. Since it has been found from our repeated experiments that cinnamaldehyde itself failed to give the reaction, it was quite pertinent to reinvestigate the reaction. Moreover, synthetic as well as mechanistic interests in this reaction prompted us to take up a systematic study of new 2*H*-thiopyran compounds using various substituted benzaldehydes. The reactions were conducted to determine the factors involved in the product formation as well as to extend the scope of the reaction. A microwave irradiation technique has also been successfully used for carrying out several of these reactions.

RESULTS AND DISCUSSION

Six aromatic aldehydes were used successfully as substrates viz. benzaldehyde (**1**), *4*-methylbenzaldehyde (**3**), *3*- methylbenzaldehyde (**5**), *4*-methoxybenzaldehyde (**7**), *2*-methoxybenzaldehyde (**9**), and veratraldehyde (**11**) (Scheme 1). *4*-Chloro, *4*-bromo, and *4*-nitrobenzaldehyde, however, failed to undergo the reaction. In all the reactions, thiopyran compounds were the major products, and the yields were around 50–60%. Some of the corresponding benzoic acids and benzyl alcohols



(**1**) R_1=H; R_2=H; R_3=H
(**2**) R_1=H; R_2=H; R_3=H
(**3**) R_1=H; R_2=H; R_3=CH_3
(**4**) R_1=H; R_2=H; R_3=CH_3
(**5**) R_1=H; R_2=CH_3; R_3=H
(**6**) R_1=H; R_2=CH_3; R_3=H
(**7**) R_1=H; R_2=H; R_3=OCH_3
(**8**) R_1=H; R_2=H; R_3=OCH_3
(**9**) R_1=OCH_3; R_2=H; R_3=H
(**10**) R_1=OCH_3; R_2=H; R_3=H
(**11**) R_1=H; R_2=OCH_3; R_3=OCH_3
(**12**) R_1=H; R_2=OCH_3; R_3=OCH_3

SCHEME 1

were also formed following a Cannizzaro reaction. The structures of all the compounds were established by various spectroscopic analyses, particularly FT-IR, 300 MHz ^{1}H NMR, and 75.5 MHz ^{13}C NMR. The ^{1}H NMR spectra of all the thiopyran compounds showed that olefinic proton H-4 appeared at $\sim\delta$ 7.0 ppm, the benzylic proton H-2 adjacent to the heteroatom appeared at $\sim\delta$ 4.5 ppm, whereas two benzylic proton (AB pattern), somewhat differentiated being near to a chiral center, appeared in the region $\sim\delta$ 3–4 ppm.

The spectroscopic data of compound (**4**) are discussed below as a representative example of this series. The structure of (**4**) was confirmed finally by an X-ray crystallographic analysis.

The UV spectrum of (**4**) showed absorption maxima at 368 nm (log ε: 3.79) and at 266 nm (log ε: 4.14), indicating the presence of extended conjugation and aromatic ring, respectively. IR spectrum of (**4**) showed strong absorption band at 1650 cm^{-1}, indicating the presence of conjugated carbonyl group. Medium intensity bands at 2916, 2852 cm^{-1} revealed the presence of –CH_2– stretching. A weak absorption band at 2743 cm^{-1} showed the presence of H-CO group, whereas a strong intensity band at 1206 cm^{-1} indicated the presence of benzylic group, and the absorption band at 819.5 cm^{-1} indicated the presence of 1,4-disubstituted benzene ring.

This structure was further supported by mass spectral fragmentation (**4**), which showed the expected M^+ peak at m/z 410. Characteristic peaks were obtained at m/z 381 [M^+-CHO], 319 [$M^+-C_6H_4CH_3$], 305 [$M^+-CH_3C_6H_4CH_2$], 277 [305—CO].

The 300 MHz ^{1}H NMR spectrum of the compound (**4**) showed that H-2 adjacent to the heteroatom appeared as singlet at δ 4.54 ppm, while two other benzylic protons (AB pattern) near to a chiral center were differentiated and appeared as doublets at δ 3.69 and 3.35 ppm (J_{AB} = 15.2 Hz). The olefinic proton H-4 appeared as singlet at δ 7.02 ppm, and the aldehyde proton as a singlet at δ 9.47 ppm. The three methyl groups appeared as three singlets at δ 2.39, 2.38, and 2.37 ppm. Twelve aromatic protons appeared in two sets of six doublets at δ 7.26 ppm (J = 8.0 Hz) and δ 7.20 ppm (J = 8.0 Hz). Thus it was clear that three *4*-methylphenyl moieties were present and are connected to the thiopyran ring system. From the ^{1}H NMR shift of H-2 (δ 4.54 ppm, singlet), it was reasonable to assume that one of these aryl groups was present as S-CH-$C_6H_4CH_3$-*4* moiety in the thiopyran ring. The molecule also contains a conjugated aldehyde group and one olefinic proton. The 75.5 MHz ^{13}C NMR assignments of compound (**4**) showed the presence of one olefinic carbon at δ 119.7 ppm, two benzylic carbons at δ 46.0 (methine) and 42.0 ppm (methylene), and three methyl signals (δ 20.9, 20.91, and 21.1 ppm). The presence of eight

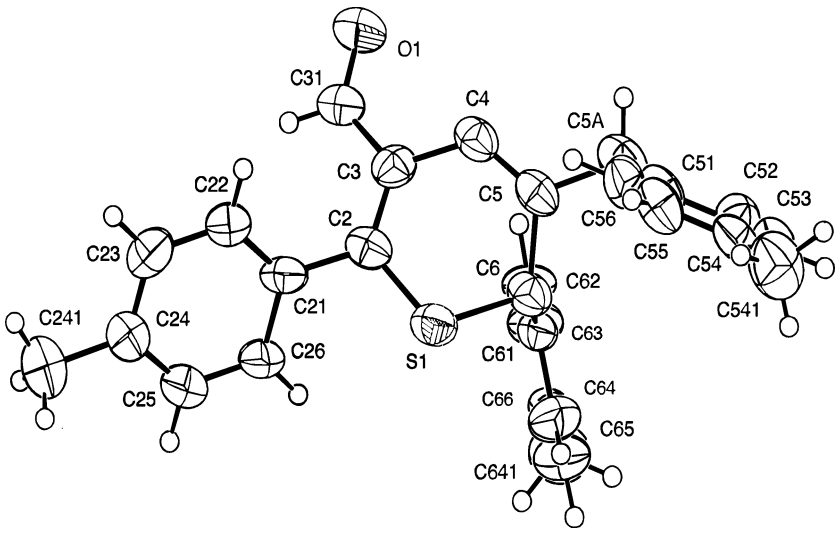


FIGURE 1 X-ray crystallogaphic structure of **4** (ORTEP projection). Ellipsoids are drawn at the 50% probability level, hydrogen atoms are given as open circles with arbitrary radii.

quaternary carbons and six different types of aromatic methines was evident from the comparison of fully decoupled spectrum with DEPT-135. The most downfield carbon, obviously the carbonyl carbon, appeared at δ 186.0 ppm. Assignment of the aromatic carbon of all the three rings "A," "B," and "C" could be made on the basis of intercomparison with the other products and the use of additivity[16] parameters. From all these observations as well as the structure of the compound reported[14] earlier, it may be concluded that the reaction of *4*-methylbenzaldehyde with sodium sulfide in aqueous ethanol gave 3-(*4*-methylbenzyl)-2,6-di(*4*-methylphenyl)-2*H*-thiopyran-5-carboxaldehyde (**4**).

The structural features of the compound (**4**) were finally confirmed by X-ray crystallographic analysis. Crystal data refinement parameters are presented in Table I. The ORTEP projection is shown in Figure 1, and some selected bond angles and lengths are presented in Table II. The X-ray crystallographic analysis of (**4**) showed it to possess a six-membered, sulfur-containing ring. As this ring is non-aromatic having a diene moiety, it showed a rather important off-plane bending. As a result the tolyl group at C(2) comes appreciable out of the plane.

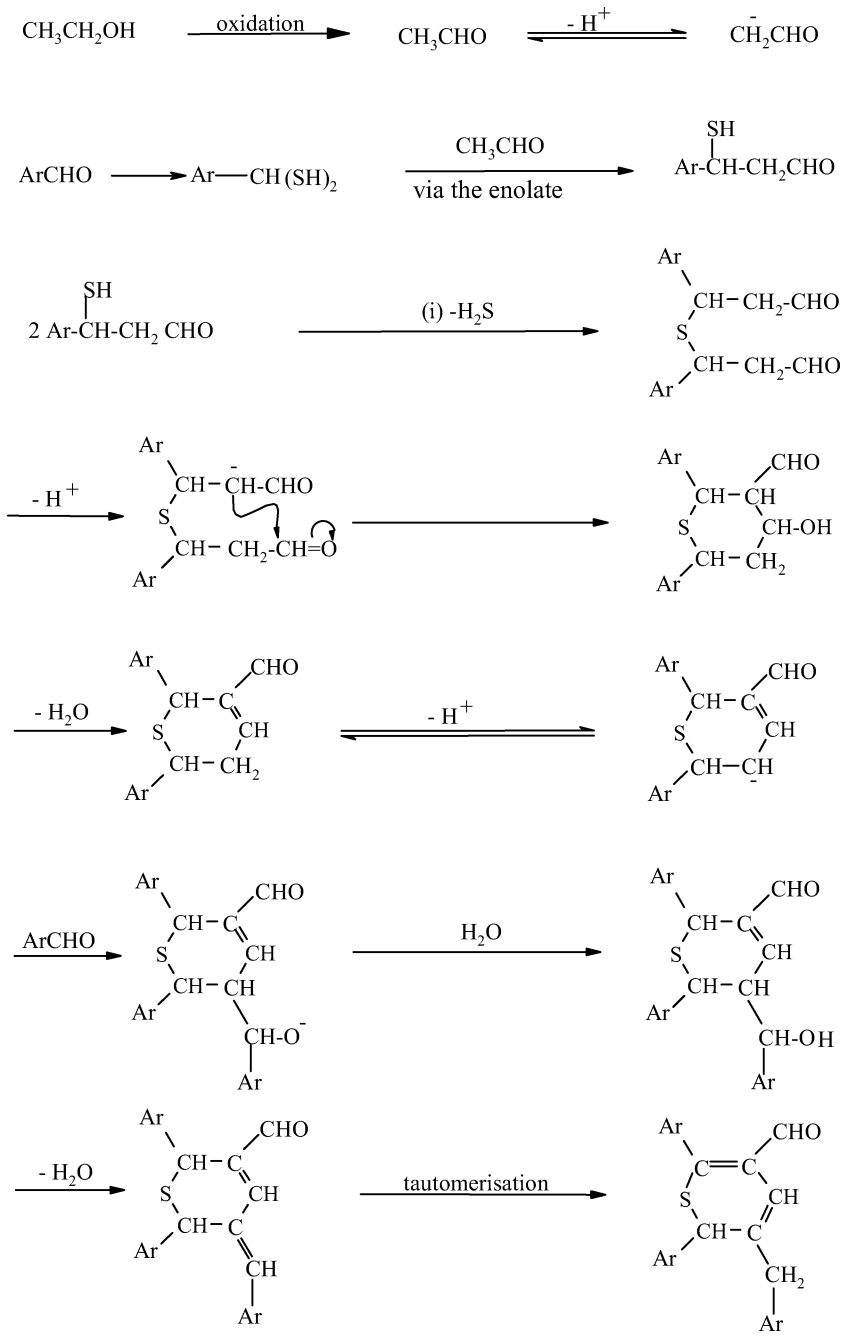
The structure of 3-benzyl-2,6-diphenyl-2*H*-thiopyran-5-carboxaldehyde (**2**) was proposed by Cremer and Subbaratnam[15] from the spectroscopic studies, and later was confirmed by X-ray

TABLE I Crystal Structure and Data Refinement Parameters for Compound 4

Compound	**4**
Empirical formula	$C_{28}H_{26}OS$
Formula weight	410.55
Crystal system/space group	$P2_1/n$
a/Å	12.351(2)
b/Å	11.141(2)
c/Å	17.193(2)
α/°	90
β/°	94.28(5)
γ/°	90
V/Å^3	2359.2(6)
Z	4
D $_{calc}$ (g/cm^3)	1.156
μ (mm^{-1})	0.153
Crystal size (mm)	0.4 × 0.2 × 0.2
Color/shape	Yellowish
Temp (K)	293
Theta range for collection	2.10–29.82
Reflections collected	12236
Independent reflections	6138
Data/restraints/parameters	2470 / 273
Goodness of fit on F^2	0.941
Final R indices [I > 2σ(I)]	0.0672
R indices (all data)	0.0880
Largest difference peak/hole	+0.21/–0.42

crystallography. In the mechanism proposed by Cremer and Subbaratram, the intermediacy of cinnamaldehyde was postulated. Since, it has been found that cinnamaldehyde itself failed to give the reaction; a modified scheme has been proposed (Scheme 2). It is proposed that $ArCH(SH)_2$ is reversibly formed from the arylaldehyde in the reaction medium, which contains large amounts of SH^- ions. This then participates in the reaction, as shown in Scheme 2.

Apart from the thermal synthesis of thiopyran compound, a modified procedure applying microwave irradiation technique was also explored. The reaction of some substituted benzaldehydes viz. *4*-methylbenzaldehyde, *3*-methylbenzaldehyde, and *2*-methoxybenzaldehyde to give corresponding thiopyran compounds also yielded the same products under microwave irradiation conditions. Yields were 50–60% after 30 min of microwave irradiation. *4*-Chloro, *4*-bromo, and *4*-nitrobenzaldehyde again failed to give the thiopyran compounds under microwave irradiation conditions.



SCHEME 2

TABLE II Selected Bond Lengths (Å) and Angles (°) for 4

S1	-C2	1.732 (6)	S1	-C6	1.832 (6)	C2	-C3	1.375 (7)
C2	-C21	1.489 (8)	C21	-C22	1.366 (7)	C21	-C26	1.415 (7)
C22	-C23	1.395 (8)	C23	-C24	1.404 (8)	C24	-C25	1.363 (8)
C24	-C241	1.533 (9)	C25	-C26	1.388 (8)	C3	-C31	1.426 (7)
C3	-C4	1.465 (7)	C31	-O1	1.236 (7)	C4	-C5	1.323 (7)
C5	-C5A	1.520 (7)	C5	-C6	1.544 (7)	C5A	-C51	1.533 (9)
C51	-C52	1.343 (8)	C51	-C56	1.356 (9)	C52	-C53	1.407 (10)
C53	-C54	1.374 (10)	C54	-C55	1.377 (9)	C54	-C541	1.517 (9)
C55	-C56	1.385 (8)	C6	-C61	1.532 (8)	C61	-C62	1.368 (8)
C61	-C66	1.389 (7)	C62	-C63	1.389 (8)	C63	-C64	1.382 (8)
C64	-C65	1.352 (9)	C64	-C641	1.513 (9)	C65	-C66	1.392 (9)
C2	-S1	-C6	104.1 (3)	C3	-C2	-C21	124.9 (5)	
C3	-C2	-S1	121.7 (4)	C21	-C2	-S1	113.1 (4)	
C22	-C21	-C26	118.7 (6)	C22	-C21	-C2	122.6 (5)	
C26	-C21	-C2	118.6 (5)	C21	-C22	-C23	121.6 (5)	
C22	-C23	-C24	120.0 (6)	C25	-C24	-C23	117.8 (6)	
C25	-C24	-C241	123.3 (6)	C23	-C24	-C241	118.9 (6)	
C24	-C25	-C26	123.1 (6)	C25	-C26	-C21	118.8 (5)	
C2	-C3	-C31	121.6 (5)	C2	-C3	-C4	120.7 (5)	
C31	-C3	-C4	117.6 (5)	O1	-C31	-C3	124.8 (6)	

In conclusion, a detailed study regarding the synthetic as well as mechanistic aspects of the reaction between benzaldehydes with sodium sulfide has been carried out which reveals that, first, *4*-chloro, *4*-bromo, and *4*-nitrobenzaldehyde failed to undergo the reaction either by the thermal procedure or the microwave irradiation technique. Hence it can be concluded that the reaction does not occur with electron-withdrawing substituents on the aromatic ring. It may be due to the fact that the presence of strong –I group at the *4*-position of benzaldehydes makes the aromatic ring much more electron deficient, and consequently it becomes more reactive towards nucleophiles. Thus in spite of producing the expected compound, it reacts differently to yield other products following Cannizaro pathway. Second, cinnamaldehyde, proposed earlier as an intermediate,[14] also failed to undergo the reaction. This clearly indicated the necessity to introduce a new mechanistic pathway.

EXPERIMENTAL

Melting points were recorded on an electrically heated Köfler Block apparatus and are uncorrected. Column and thin layer chromatography were carried out using silica gel (Qualigens 60–120 mesh, Spectrochem 60–120, and 100–200 mesh) and silica gel G (Spectrochem and SRL),

respectively. Anhydrous sodium sulfate was used for drying extracts. The analytical samples were routinely dried over $CaCl_2$ in vacuo at room temperature. The aldehydes used were A.R. reagents obtained from Merck, Aldrich, and Spectrochem (India). Purities were checked by ^{1}H NMR spectroscopy. Sodium sulfide decahydrate ($Na_2S.10H_2O$) obtained from Spectrochem (India) was used for these reactions. IR spectra were recorded in KBr discs on a Perkin-Elmer RXI FT-IR spectrometer. UV spectra were measured on a Hitachi U-3501 spectrophotometer and the mass spectra (EI-MS) were recorded with a JEOL JMS 1600 mass spectrometer. Elemental analyses (C, H, S) were conducted using the Perkin-Elmer 2400 Series II elemental analyzer and results were found to be in good agreement ($\pm$ 0.2%) with the calculated values for C, H, S. NMR spectra were usually recorded in $CDCl_3$ solution on a Bruker AM-300L at the Departmental facilities—a super conducting Oxford magnet NMR spectrometer (7.5 Tesla) equipped with an ASPECT-3000 computer, an array processor, and a sophisticated process controller. These spectra were recorded using a switchable 5 mm ^{1}H-^{13}C dual probes at ambient temperature and operating with the Bruker DISR 861 and DISR 871 software. The spectrometer frequencies in the Bruker AM-300L are 300.133 MHz for ^{1}H NMR and 75.457 MHz for ^{13}C NMR. Some spectra were also recorded with a Bruker DRX 500 NMR spectrometer (11.7 Tesla), equipped with a Silicon Graphics INDY computer. These spectra were recorded in BBI (broad band inverse) probe with 5 mm NMR sample tube at 27°C temperature. The actual spectrometer frequencies are 500.134 MHz and 125.770 MHz, respectively, for ^{1}H and ^{13}C NMR in the instrument. X-ray crystallographic data were recorded with an automatic NONIUS CAD-4 diffractometer. All recordings are at room temperature. X-ray crystallographic data were recorded with an automatic NONIUS CAD-4 diffractometer. The wavelength of MoKα radiation was 0.7107 Å. The structure were solved by direct methods and refined with the SHELXL program.[17] Data collection was performed at room temperature. The crystals were monoclinic; space group $P2_1/n$. An ORTEP projection is shown in Figure 1. Crystallographic data for compound **4** have been deposited with the Cambridge Crystallographic Data Centre as CCDC 248039. Copies of the data can be obtained, free of charge, on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK (fax: +44 1223 336033 or e-mail: deposit@ccdc.cam.ac.uk).

General Method

The benzaldehyde or substituted benzaldehyde was taken with a 1:3 molar ratio of sodium sulfide in aqueous ethanol (1:1). The mixture

was refluxed on an oil bath for 3–7 h with continuous stirring. The reactions were monitored by TLC and ^{1}H NMR spectroscopy. The reaction mixture was then cooled and kept standing overnight at room temperature and then extracted with ether (3 × 50 mL). The post-reaction mixture was concentrated under reduced pressure, and the residue was chromatographed over silica gel [petroleum ether (60–80°C)/ benzene].

Microwave Irradiation Assisted Procedure

The reactants, in the proportions mentioned above, were subjected to microwave irradiation via a microwave oven (BMO-700T) operating at a power of ~1000 watts for 30 min. A modified apparatus with a reflux condenser was used.

Reaction of Benzaldehyde (1) with Sodium Sulfide in Aqueous Ethanol: 3-Benzyl-2,6-diphenyl-2H-thiopyran-5-carboxaldehyde (2; $C_{25}H_{20}SO$)

Benzaldehyde (2.65 g, 0.025 mol) and sodium sulfide (18 g, 0.075 mol) were reacted in aqueous ethanol (1:1, 100 mL) under reflux for 4 h. Column chromatography over silica gel [10% benzene in petroleum ether (60–80°C)] yields yellow crystals, mp 144°C; yield: 1.68 g (55%); IR: ν = 2842.5 (m, $-CH_2$-), 1641.5 (s, aldehyde >C=O), 1208.5 (s, benzylic), 733.5, 696.5 (m, monosubstituted benzene ring); cm^{-1}; UV: λ_{max} (log ε) = 365.5 (4.15) and 267 (4.64) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.54 (1H, s, H-2), 7.02 (1H, s, H-4), 3.72 and 3.38 (1H, d, J = 15.2 each benzylic methylene), 9.43 (1H, s, $-C\underline{H}O$), 7.34–7.27 (15H, m, H-A,B,C) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 46.2 (C-2), 138.3 (C-3), 120.0 (C-4), 154.5 (C-5), 140.9 (C-6), 42.6 ($-CH_2$-, benzylic), 186.5 (-$\underline{C}$HO), 132.0 (A,C-1), 129.0 (A,C-2,6), 128.9 (A,C-3,5), 128.1 (A,C-4), 128.8 (B,C-1), 127.3 (B,C-2,6), 128.2 (B,C-3,5), 126.7 (B,C-4), 133.9 (C,C-1), 131.1 (C,C-2,6), 129.1 (C,C-3,5), 130.3 (C,C-4) ppm: MS (EI): m/z = 368 (M^+), 339 (M^+-CHO), 292 [$M^+-C_6H_5$ + H$^\bullet$], 277 [M^{+-} $C_6H_5CH_2^\bullet$], 247 (277—CHO-H$^\bullet$), 215 [$M^+-2C_6H_5$ + H$^\bullet$], 121 (Ph-CS^+), 91 ($C_7H_7^+$). Anal. Calcd. For $C_{25}H_{20}SO$: C, 81.73; H, 5.50; S, 8.75, Found: C, 81.65; H, 5.44; S, 8.70.

Reaction of 4-Methylbenzaldehyde (3) with Sodium Sulfide in Aqueous Ethanol: 3-(4-Methylbenzyl)-2,6-di(4-methylphenyl)-2H-thiopyran-5-carboxaldehyde (4; $C_{28}H_{26}SO$)

4-Methylbenzaldehyde (3 g, 0.025 mol) was reacted with sodium sulfide (18 g, 0.075) in the presence of aqueous ethanol (1:1, 100 mL) for 4 h. Column chromatography over silica gel yields [10% benzene in petroleum ether (60–80°C)] yellow crystals, mp 130°C; yield 2.05 g

(60%).; IR: ν = 2916, 2853 (m, $-CH_2-$), 1650.5 (s, aldehyde >C=O), 1206 (s, benzylic), 819.5 (s, 1,4-disubstituted benzene ring); cm^{-1}; UV: λ_{max} (log ε) = 368 (3.79) and 266 (4.14) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.54 (1H, s, H-2), 7.02 (1H, s, H-4), 3.69 and 3.35 (1H, d, J = 15.2, each, benzylic methylene), 2.39, 2.38, 2.37 (3H, s each, three-C$\underline{H}_3$), 9.47 (1H, s, $-C\underline{H}O$), 7.26 (6H, d, J = 8.0, A,B,C,H-2,6), 7.20 (6H, d, J = 8.0, A,B,C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 46.0 (C-2), 138.1 (C-3), 119.7 (C-4), 154.6 (C-5), 140.6 (C-6), 42.0 ($-CH_2$-, benzylic), 20.90, 20.91, 21.10 (3-$\underline{C}H_3$), 186.4 (-$\underline{C}$HO), 136.1 (A,C-1), 128.8 (A,C-2,6), 130.9 (A,C-3,5, overlapped signal), 137.7 (A,C-4), 128.5 (B,C-1), 127.2 (B,C-2,6), 130.9 (B,C-3,5, overlapped signal), 137.5 (B,C-4), 131.1 (C,C-1), 130.9 (C,C-2,6, overlapped signal), 128.9 (C,C-3,5), 136.3 (C,C-4) ppm: MS (EI): m/z = 410 (M^+), 381 (M^+-CHO), 319 [$M^+-C_6H_4CH_3$], 305 [$M^+-CH_3C_6H_4CH_2$], 277 (305—CO), 229 (319—$C_6H_4CH_3$ + $H^\bullet$), 215 (229—$CH_3C_6H_4CH_2$+ $H^\bullet$), 135 [M^+—$C_{20}H_{18}O$], 105 [$M^+-C_{20}H_{17}SO$], 91 ($C_7H_7^+$). Anal. Calcd. For $C_{28}H_{26}SO$: C, 82.15; H, 6.40; S, 7.83, Found: C, 81.95; H, 6.33; S, 7.75.

Reaction of 3-Methylbenzaldehyde (5) with Sodium Sulfide in Aqueous Ethanol: 3-(3-Methylbenzyl)-2,6-di(3-methylphenyl)-2H-thiopyran-5-carboxaldehyle (6; $C_{28}H_{26}SO$)

3-Methylbenzaldehyde (0.3 g, 0.0025 mol) and sodium sulfide (1.98 g, 0.0075 mol) were reacted in aqueous ethanol (1:1, 100 mL) for 6 h. Column chromatography over silica gel yields [20% benzene in petroleum ether (60–80°C)] yellowish amorphous solid, mp 116°C; yield 0.18 g (53%); IR: ν = 2919.5, 2853.5 (m, $-CH_2$-), 1658.5 (s, aldehyde >C=O), 1208.5 (s, benzylic), 786.5, 756.5 (s, 1,3-Disubstituted benzene ring); cm^{-1}; UV: λ_{max} (log ε) = 366 (3.09) and 264 (3.48) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.50 (1H, s, H-2), 7.00 (1H, s, H-4), 3.66 (1H, d, J = 15, benzylic), 3.32 (1H, d, J = 15, benzylic), 2.33 (9H, s, 3-C$\underline{H}_3$), 9.42 (1H, s, $-C\underline{H}O$), 7.05 (3H, s, A,B,C,H-2), 7.15 (3H, d, J = 4.1, A,B,C,H-4), 7.23 (3H, br t, A,B,C,H-5), 7.24 (3H, d, J = 5.3, A,B,C,H-6) ppm; ^{13}C NMR ($CDCl_3$, δ, 125.5 MHz): 46.00 (C-2), 138.6 (C-3), 120.1 (C-4), 155.8 (C-5), 141.5 (C-6), 42.9 ($-CH_2$-, benzylic), 21.9, 21.8, 21.6 (3-$\underline{C}H_3$), 187.2 (-$\underline{C}$HO), 138.9 (A,C-1), 131.6 (A,C-2), 134.2 (A,C-3), 128.5 (A,C-4), 126.5 (A,C-5), 129.2 (A,C-6), 128.8 (B,C-1), 130.3 (B,C-2), 133.5 (B,C-3), 128.3 (B,C-4), 124.8 (B,C-5), 128.7 (B,C-6), 138.7 (C,C-1), 132.0 (C,C-2), 132.1 (C,C-3), 128.6 (C,C-4), 127.9 (C,C-5), 129.3 (C,C-6) ppm. Anal. Calcd. For $C_{28}H_{26}SO$: C, 82.15; H, 6.40; S, 7.83, Found: C, 82.0; H, 6.30; S, 7.70.

Reaction of 4-Methoxybenzaldehyde (7) with Sodium Sulfide in Aqueous Ethanol: 3-(4-Methoxy-benzyl)-2,6-di(4-methoxyphenyl)-2H-thiopyran-5-carboxaldehyde (8; $C_{28}H_{26}SO_4$)

4-Methoxybenzaldehyde (4.08 g, 0.03 mol) was reacted with sodium sulfide (21.6 g, 0.09 mol) in aqueous ethanol (1:1, 120 mL) under refluxing conditions for 6 h. Column chromatography [5% benzene in petroleum ether (60–80°C)] over silica gel yields yellow amorphous solid (mp 151°C); yield 2.42 g (53%).; IR: $\nu = 2924.5, 2839.5$ (m, $-CH_2$-), 1651.5 (s, aldehyde >C=O), 1250 (s, C—O—C group), 829 (s, 1,4-disubstituted benzene ring); cm^{-1}; UV: λ_{max} (log ε) = 361 (3.45), 267 (3.68) and 227 (3.95) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.55 (1H, s, H-2), 7.10 (1H, s, H-4), 3.63 (1H, d, J = 15.3, benzylic), 3.30 (1H, d, J = 15.3, benzylic), 3.78 (9H, s, three-C$\underline{H}_3$), 9.40 (1H, s, —C$\underline{H}$O), 7.25 (6H, d, J = 8.5, A,B,C,H-2,6), 6.86 (6H, d, J = 8.5, A,B,C,H-3,5) ppm; ^{13}C NMR ($CDCl_3$, δ, 75.5 MHz): 45.80 (C-2), 133.0 (C-3), 119.6 (C-4), 154.5 (C-5), 133.3 (C-6), 64.60 (—CH_2-, benzylic), 55.10 (3-O$\underline{C}H_3$), 186.6 (-$\underline{C}$HO), 130.4 (A,C-1), 128.4 (A,C-2,6, overlapped signal), 114.3 (A,C-3,5), 159.4 (A,C-4), 126.1 (B,C-1), 128.4 (B,C-2,6, overlapped signal), 113.9 (B,C-3,5), 159.1 (B,C-4), 132.5 (C,C-1), 128.4 (C,C-2,6, overlapped signal), 114.1 (C,C-3,5), 161.6 (C,C-4) ppm. Anal. Calcd. For $C_{28}H_{26}SO_4$: C, 73.36; H, 5.67; S, 6.98, Found: C, 73.15; H, 5.50; S, 6.82.

Reaction of 2-Methoxybenzaldehyde (9) with Sodium Sulfide and Ethanol in Water: 3-(2-Methoxybenzyl)-2,6-di(2-methoxyphenyl)-2H-thiopyran-5-carboxaldehyde (10; $C_{28}H_{26}SO_4$)

2-Methoxybenzaldehyde (0.68 g, 0.005 mol) and sodium sulfide (3.87 g, 0.015 mol) were reacted in aqueous ethanol (1:1, 20 mL) under refluxing conditions for 6 h. Column chromatography [5% benzene in petroleum ether (60–80°C)] over silica gel yields afforded the compound **10** as yellow amorphous solid, mp 125°C; yield 0.38 g (57%); IR: ν = 2935, 2837.5 (m, $-CH_2$-), 1659 (s, aldehyde >C=O), 1246.5 (s, C—O—C group), 751.5 (s, 1,2-disubstituted benzene ring); cm^{-1}; UV: λ_{max} (log ε) = 368 (3.26), 262.5 (3.58) and 244.7 (3.64) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 5.10 (1H, s, H-2), 7.20 (1H, s, H-4), 3.52 (1H, d, J = 15.4, benzylic), 3.45 (1H, d, J = 15.4, benzylic), 3.72 (9H, s, three-OC$\underline{H}_3$), 9.21 (1H, s, —C$\underline{H}$O), 6.80–6.90 (9H, m, A,B,C,H-3,4,5), 7.24 (3H, d, J = 8.0, A,B,C,H-6) ppm; ^{13}C NMR ($CDCl_3$, δ, 125.5 MHz): 39.65 (C-2), 129.5 (C-3), 120.1 (C-4), 158.0 (C-5), 133.7 (C-6), 37.12 (—CH_2-, benzylic), 56.05, 55.86, 55.50 (3-O$\underline{C}H_3$), 187.8 (-$\underline{C}$HO), 128.8 (A,C-1), 156.0 (A,C-2), 132.0 (A,C-3), 120.7 (A,C-4), 129.0 (A,C-5), 111.0 (A,C-6), 128.6

(B,C-1), 150.0 (B,C-2), 131.0 (B,C-3), 120.3 (B,C-4), 128.2 (B,C-5), 110.6 (B,C-6), 131.2 (C,C-1), 157.0 (C,C-2), 134.0 (C,C-3), 120.8 (C,C-4), 131.4 (C,C-5), 112.0 (C,C-6) ppm. Anal. Calcd. For $C_{28}H_{26}SO_4$: C, 73.36; H, 5.67; S, 6.98, Found: C, 73.21; H, 5.56; S, 6.75.

*Reaction of Veratraldehyde (11) with Sodium Sulfide in Aqueous Ethanol: 3-(3,4-Dimethoxybenzyl)-2,6-di(3,4-dimethoxyphenyl)-2*H*-thiopyran-5-carboxaldehyde (12; $C_{31}H_{32}SO_7$)*

Veratraldehyde (0.83 g, 0.005 mol) was reacted with sodium sulfide (3.87 g, 0.015 mol) in aqueous ethanol (1:1, 20 mL) for 7 h. Column chromatography [10% benzene in petroleum ether (60–80°C)] over silica gel yields afforded the pure compound **12** as yellow amorphous solid, mp 160°C; yield 0.45 g (50%); IR: ν = 2937.5, 2841.5 (m, $-CH_2$-), 1681.5 (s, aldehyde >C=O), 1269.8 (s, C—O—C group), cm^{-1}; UV: λ_{max} (log ε) = 338.5 (3.73), and 231.5 (3.93) nm; ^{1}H NMR ($CDCl_3$, δ, 300 MHz): 4.50 (1H, s, H-2), 7.00 (1H, s, H-4), 3.66 and 3.53 (1H, d, each, J = 15.4, benzylic), 3.91 (18H, s, 6-OC$\underline{H}_3$), 9.47 (1H, s, —C$\underline{H}$O), 7.01 (1H, s, A, H-2), 6.70 (1H, d, J = 10.3, A, H-5), 6.90 (1H, d, J = 10.3, A,H-6), 7.25 (1H, s, B,H-2), 6.60 (1H, d, J = 15.8, B,H-5), 7.50 (1H, d, J = 15.8, B,H-6), 7.03 (1H, s, C,H-2), 6.80 (1H, d, J = 8.3, C,H-5), 7.45 (1H, d, J = 8.3, C,H-6) ppm; ^{13}C NMR ($CDCl_3$, δ, 125.5 MHz): 46.50 (C-2), 144.5 (C-3), 120.0 (C-4), 155.7 (C-5), 143.9 (C-6), 42.40 ($-CH_2$-, benzylic), 56.30 (6-O$\underline{C}H_3$), 187.1 (-$\underline{C}$HO), 127.7 (A,C-1), 125.1 (A,C-2), 132.4 (A,C-3), 149.4 (A,C-4), 112.6 (A,C-5), 120.4 (A,C-6), 126.6 (B,C-1), 123.4 (B,C-2), 131.2 (B,C-3), 149.3 (B,C-4), 111.6 (B,C-5), 120.2 (B,C-6), 128.7 (C,C-1), 125.6 (C,C-2), 133.5 (C,C-3), 151.7 (C,C-4), 114.4 (C,C-5), 121.5 (C,C-6) ppm. Anal. Calcd. For $C_{31}H_{32}SO_7$: C, 67.75; H, 6.01; S, 5.82, Found: C, 67.62; H, 5.85; S, 5.70.

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